

Original article

Asthma during the primary school ages – prevalence, remission and the impact of allergic sensitization

Background: Childhood is the most important time for asthma development. The aims of this study were to study changes in prevalence of asthma and wheeze, remission of asthma and changes in risk factor pattern from age 7–8 to age 11–12 in a cohort of school children.

Methods: In 1996, 3525 children aged 7–8 years in northern Sweden were invited to participate in a parental expanded ISAAC questionnaire survey. The cohort has been followed prospectively with yearly follow-ups to age 11–12, with a 97% yearly response rate. Skin prick tests were conducted at age 7–8 and 11–12.

Results: The prevalence of *physician-diagnosed asthma* increased from 5.7% at age 7–8 to 7.7% at age 11–12. Life-time prevalence of *wheeze* was 34.7% at age 11–12. The remission of asthma was 10% yearly and inversely related to allergic sensitization. Relapses were common, and remission persisting throughout the observation period was 5% yearly. Allergic sensitization was associated with *current asthma* at age 7–8 [adjusted odds ratio (OR) 4.9 (95% confidence interval (CI) 3.3–7.3)] and when the children were 4 years older [OR 5.6 (3.9–8.2)]. A family history of asthma was associated with *current asthma* at age 7–8 [OR 3.0 (2.1–4.5)] and 11–12 [OR 2.8 (2.0–3.9)]. Ever having lived with a cat was significantly negatively associated with *current asthma*.

Conclusions: The prevalence of asthma increased continuously during the primary school ages. Among several significant risk factors, allergic sensitization and a family history of asthma were the most important. With increasing age many known risk factors lost significance. Remission was inversely related to allergic sensitization.

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There is strong evidence that the prevalence of asthma and wheezing conditions among children has been rising globally for at least four decades (1, 2), although recent data indicate a plateau may have been reached (3). This rising trend is only in part due to changed diagnostic practice (4). Trends in Sweden parallel those in the rest of the Westernized world (5–7). Childhood has been proposed as the most important time for development of both wheezing and allergic conditions (8–11). To date research has primarily focused on the infant's first years of life, and also on the long-term outcome of childhood asthma into adulthood (8, 12). Asthma during school age has not been as extensively studied. This time period includes both the transition from childhood wheeze to adult asthma and changes in environmental exposures.

Many risk factors for childhood asthma have been identified, although the recent increase in prevalence has been linked to the comprehensive concept of a 'Westernized lifestyle'. Current evidence has found allergic sensitization, family history of asthma, severe respiratory tract infections, low birth weight, and pollutants such as

parental (mother's) tobacco smoke to be important risk factors for childhood asthma (6, 9, 12–15). High exposure to some allergens (e.g. keeping furred pets) has been postulated as a protective factor (9, 15, 16). In contrast, avoidance strategies for other allergens (e.g. dust mite) have shown clinical benefits on asthma symptoms (17). Because pet allergens are passively transferred on clothing to schools, mandatory school attendance means an unavoidable contact with pet allergens (9, 18). Asthma is not a single disease entity, and the heterogeneity of the asthma phenotypes seems to be prominent early in life (11, 14, 19). The allergic asthma phenotype differs from the nonallergic asthma phenotypes with respect to age at onset, severity of symptoms and long-term outcome (8, 12, 14).

Several cross-sectional studies have shown increased prevalence with increased age (7). To date few longitudinal population studies of school age asthma have been conducted with annual follow-ups. We present data from an ongoing cohort study of school children, followed yearly by questionnaire and skin prick tests (6). Within

this study we have previously shown a high incidence of asthma (nearly 1/100/year), that allergic asthma differs from nonallergic asthma with respect to predisposing factors, and that a cat or dog in the home tends to protect against developing type-1 allergy and asthma (9, 10, 19, 20). The aims of the present study were to examine the prevalence, incidence and remission of asthma during the period from ages 7–8 to 11–12 years and to evaluate the risk factor patterns for asthma at this time of life.

Material and methods

Study population

In 1996, all children enrolled in first- and second-grade classes (age 7–8 years) in Kiruna, Luleå and Piteå, three municipalities in the northernmost province of Sweden, Norrbotten, were invited to participate in a longitudinal study of asthma and allergic diseases.

The study started with a parental questionnaire distributed through the children's teachers, assessing prevalence of asthmatic and allergic conditions (6, 19). Of the 3525 school children invited, 3430 (97%) participated. A 97% response rate was achieved in each year until age 11–12. The children in two of the municipalities (Kiruna and Luleå, $n = 2454$) were invited to skin prick tests at age 7–8 and 11–12 (20). The participation rate was 88% at both occasions ($n = 2149$ and $n = 2155$), and in all 1870 children participated both at age 7–8 and 4 years later. Approval for the study was acquired from the ethical committee at the University Hospital of Northern Sweden in Umeå. Informed consent was obtained from the children's parents.

Questionnaire

The questionnaire was an expanded ISAAC questionnaire (21), which has been described previously (6). The same questions regarding symptoms and current exposures were used in the follow-ups. The ISAAC questionnaire has been validated internationally (22), and a clinical validation for our cohort has been published previously (19).

Skin prick tests

Skin prick testing was carried out by two nurses (KKB and LG) following the EAACI recommendations (23). The age 11–12 follow-up testing in Luleå was performed by a third nurse (AJ). All three nurses were specifically trained for this study.

Testing was performed by lancet on the forearm for each of 10 allergens: birch, timothy, mugwort, cat, dog, horse, *Dermatophagoides pteronyssinus*, *D. farinae*, *Cladosporium* and *Alternaria* (Soluprick; ALK, Hørsholm, Denmark). The potency of the allergens was 10 HEP, except for the two moulds, which had a potency of 1 : 20 w/v. Histamine 10 mg/ml and glycerol were used as positive and negative controls respectively. A mean wheal diameter of ≥ 3 mm yielded a positive result.

Definitions

The majority of the definitions have previously been presented (6, 19). Only definitions of special importance or new for this work are presented below.

Wheeze last 12 months: 'Has your child had wheezing or whistling in the chest in the last 12 months?' (21).

Current asthma: Physician-diagnosed asthma and either wheeze or use of asthma medicines during the last 12 months (6).

A family history of asthma: Mother, father or sibling reporting ever having had asthma (6).

Allergic sensitization: At least one positive skin test.

Life-time prevalence: Proportion of subjects reporting a condition in any of the five questionnaires from age 7–8 to age 11–12.

Asthma remission: Subject reporting current asthma at one occasion and reporting neither wheeze last 12 months nor use of asthma medicines at the next occasion. Remission was defined as *persisting* if no relapse of symptoms or medication occurred during the remaining study period.

Combinations of asthma and allergy

During the initial evaluation at age 7–8, four groups were identified: allergic asthmatics, allergic nonasthmatics, nonallergic asthmatics and nonallergic nonasthmatics. At the re-evaluation at age 11–12 changes between groups were studied. The analysis was limited to the 1870 individuals skin prick tested both at age 7–8 and 11–12.

Statistical analyses

Prevalence was measured each year for all children participating that year (i.e. treated as an open cohort). Calculation of risk was performed on the individuals participating at age 7–8 and 11–12 separately. Multivariate analysis was limited to the skin prick tested children.

Bivariate comparisons of prevalence of the outcomes and associated risk factors were made using chi-square test and when appropriate Fisher's exact test. Multiple logistic regression analyses included the variables significant ($P < 0.05$) or borderline significant ($P < 0.10$) in bivariate analyses either at age 7–8 or 11–12. Hence the same risk factors were assessed in multivariate analyses at both occasions. Multivariate relationships are presented as odds ratios (ORs) with 95% confidence interval (CI). All analyses were made using the Statistical Package for Social Science (SPSS) software version 11.5.0 (Chicago, IL, USA).

Results

Prevalence

The prevalence of *physician-diagnosed asthma* increased from 5.7% at age 7–8 to 7.7% at age 10–11 and 11–12 ($P < 0.001$). *Ever asthma* followed the same pattern. *Wheeze last 12 months* decreased continuously from 11.7% at age 7–8 to 9.4% at age 11–12 ($P < 0.001$). Prevalence was significantly higher among boys (Table 1).

The life-time prevalence of asthma increased more by time than the point prevalence for each year. At 11–12 years of age, 34.7% of the children had at one or more occasion reported ever having had *wheezing*, and 9.6% reported ever having had *physician-diagnosed asthma* (Fig. 1).

Remission

The *remission* rate was approximately 10% per year, of whom a half relapsed. Thus the *persisting remission* was

Table 1. Prevalence (%) of asthma and different asthma-related conditions year by year from 1996 to 2000. Differences by sex, and between year 1996 and 2000

	Study year (ages)										Difference 1996 to 2000 (<i>P</i> -value)
	1996 (7–8), <i>n</i> = 3430		1997 (8–9), <i>n</i> = 3453		1998 (9–10), <i>n</i> = 3446		1999 (10–11), <i>n</i> = 3406		2000 (11–12), <i>n</i> = 3395		
	All		All		All		All		All		
	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	
	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	
Ever asthma	6.4		7.7		8.9		9.4		9.3		<0.001
Physician-diagnosed asthma	4.9	7.8**	6.0	9.4***	6.6	11.1***	8.0	10.8**	7.7	10.9**	<0.001
	5.7		6.5		7.1		7.7		7.7		
Current asthma	4.3	7.1**	5.0	7.9**	5.4	8.7***	6.3	9.0**	6.5	9.0**	<0.001
	5.4		5.8		6.4		7.0		6.3		
Wheeze last 12 months	4.2	6.5**	4.6	6.9**	4.8	8.0***	5.6	8.3**	5.4	7.2*	0.001
	11.7		10.7		10.2		9.7		9.4		
Use of asthma medicines	10.4	12.9*	9.3	12.0*	8.2	12.1***	8.1	11.2**	8.7	10.1 NS	<0.001
	7.1		9.8		9.5		9.8		9.2		
Use of inhaled corticosteroids	6.0	8.1*	8.4	11.1**	7.3	11.6***	8.3	11.3**	7.9	10.5**	0.853
	4.3		4.0		4.3		4.7		4.5		
	3.6	5.0 NS	3.2	4.7*	3.2	5.3**	3.4	6.0***	3.5	5.4*	

P* < 0.050; *P* < 0.010; ****P* < 0.001. NS, not significant.

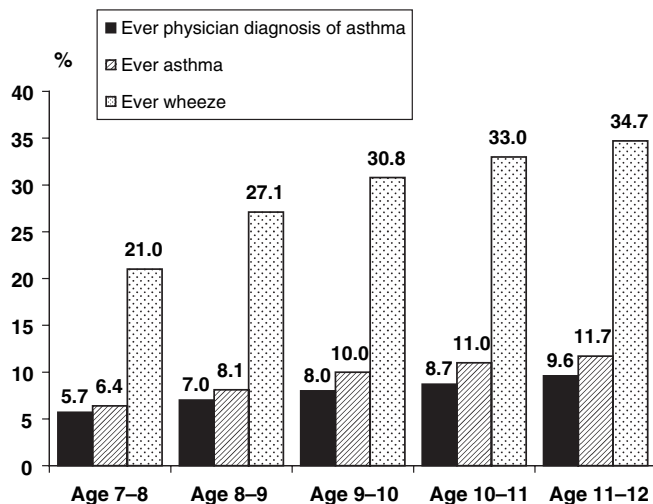


Figure 1. Life-time prevalence of asthma and wheeze, i.e. prevalence of subjects ever reporting conditions; in the current questionnaire or in a questionnaire before.

5% (Table 2). Among cases with *current asthma* at age 7–8, the 4-year remission rate was 25.5%, with no significant difference between boys (25.3%) and girls (25.8%). Four-year remission was significantly higher among the nonallergic asthmatics (44.9%) in comparison with the allergic asthmatics (17.5%, *P* < 0.001).

Combinations of asthma and allergy

Over the 4-year period, the groups *nonallergic nonasthmatics*, *allergic nonasthmatics* and *allergic asthmatics* remained largely unchanged, with 82–85% remaining in the same group. The *nonallergic asthmatic* group was

Table 2. Remittent cases of previous year's 'current asthmatics'

Age years	Asthmatics (<i>n</i>)	Remission*		Persisting remission†	
		<i>n</i>	%	<i>n</i>	%
7–8	177	–	–	–	–
8–9	194‡	18	10.2	7	4.0
9–10	213‡	20	10.3	12	6.2
10–11	221‡	16	7.5	11	5.2
11–12	215‡	26	11.8	–	–

*Remission was defined as a former 'current asthma' subject neither having asthma symptoms nor taking asthma medicines last 12 months.

†Persisting remission was defined like remission, but with neither relapse of asthma symptoms nor taking asthma medicines for the rest of the study period.

‡Based on subjects participating this and the previous year.

more dynamic, as only 40% remained within this classification. In the *allergic nonasthmatic* group, the 4-year cumulative incidence of asthma was 9%, while it was only 2% in the *nonallergic nonasthmatic* group. The incidence of allergic sensitization among incident asthmatics was 33% compared with 16% among those without incident asthma (Fig. 2).

Multivariate relationships

Sensitization to any allergen was the strongest risk factor for *current asthma*, OR 4.88 (95% CI 3.31–7.20) at age 7–8, increasing to OR 5.63 (3.88–8.18) at age 11–12 with no difference between sexes. A family history of asthma was the second strongest risk factor with OR 3.04 (2.07–4.47) for *current asthma* at age 7–8 and OR 2.78 (1.96–3.94) at age 11–12. Stratified by sex, the effect of family history was less pronounced among boys [OR 2.19 (1.34–3.69)]

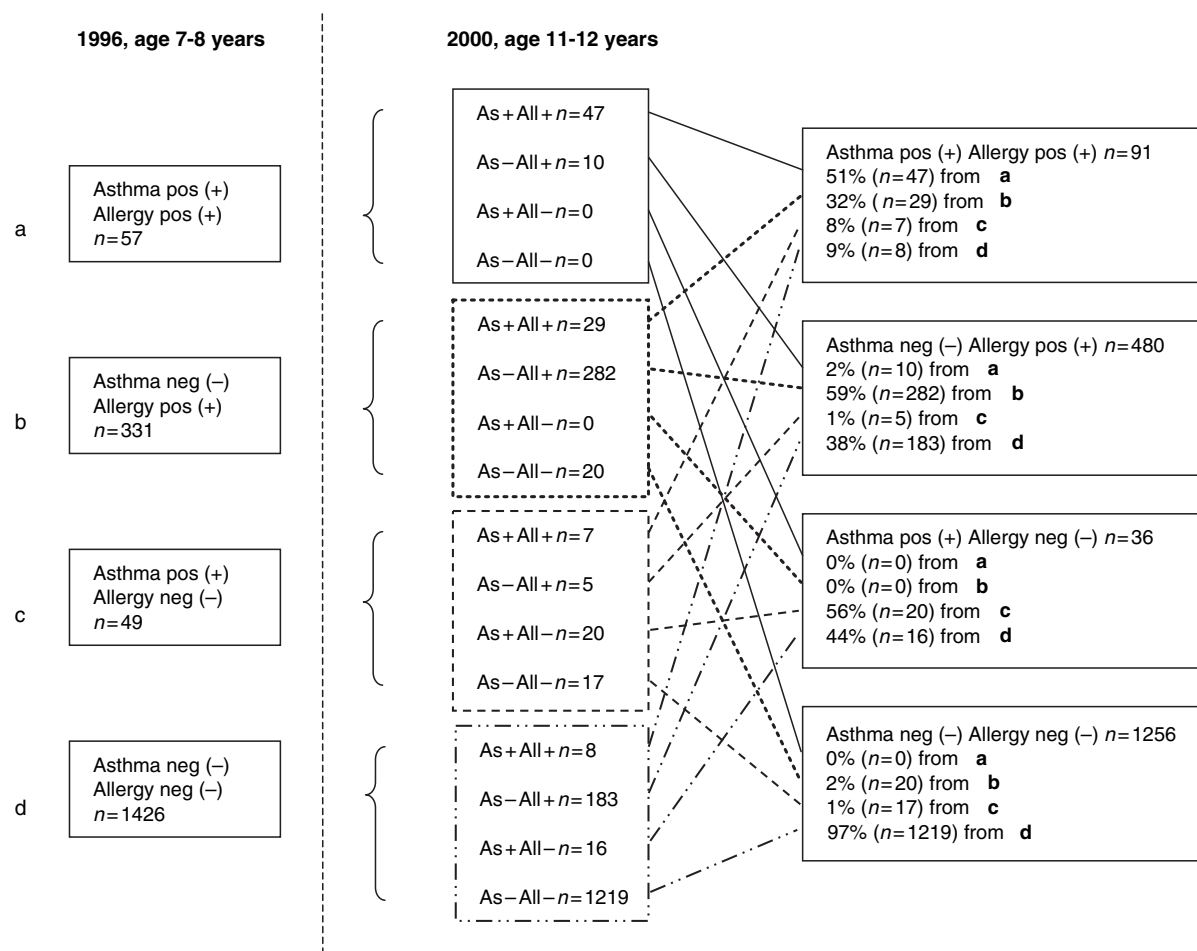


Figure 2. Disease development in subjects tested for allergic sensitization at age 7–8 and 11–12. Definitions: Allergy +/All +: any positive skin prick test; Asthma +/As +: 'current asthma'.

when compared with girls [OR 5.01 (2.68–9.36)] at age 7–8. This relationship was similar when the children were 4 years older. Low birth weight and respiratory infections were significantly associated with *current asthma*, with ORs > 2. The association between respiratory infections and *current asthma* was more pronounced among girls than boys.

Of the variables significantly associated with *current asthma* at age 7–8 only family history of asthma, cat ever at home and allergic sensitization were significantly associated with *current asthma* when the children were 4 years older. At age 11–12, ever having a cat at home was inversely associated with *current asthma*, OR 0.54 (0.34–0.86). At this age, consuming ≥ 7 citrus-fruits/week during the winter season was also significantly negatively associated with *current asthma*, OR 0.58 (0.35–0.97) compared with consuming ≤ 2 /week.

The risk factor pattern for *physician-diagnosed asthma* was similar to that for *current asthma* (Table 3). The same was true for *wheeze last 12 months*, but with lower ORs

and wider confidence intervals. At age 7–8 allergic sensitization [OR 3.19 (2.40–4.23)] and respiratory infections [OR 2.83 (2.09–3.84)] showed the strongest associations with wheeze, a pattern also observed when the children were 4 years older (Table 3). In multivariate analysis, having 'a family history of allergy' was significantly associated with all three asthma outcomes (adjusted ORs 1.6–1.8) but only at age 11–12. This variable was not included in the final multivariate models because of extensive overlap with having a family history of asthma.

Discussion

This study of a large cohort of school children followed yearly focuses on the complex relationship between allergic sensitization and asthma. The main findings were that prevalence of asthma symptoms was high at age 7–8 but decreased with age, while the proportion of symptomatic children having a diagnosis of asthma increased.

Table 3. Risk factors for prevalent cases of 'current asthma', physician-diagnosed asthma and wheeze last 12 months at age 7–8 (1996) and age 11–12 (2000) in the cohort tested for allergy ($n = 2148$ (1996) and $n = 2180$ (2000)), calculated by multiple logistic regression analysis

Independent variable	Current asthma				Physician-diagnosed asthma				Wheeze last 12 months			
	Age 7–8		Age 11–12		Age 7–8		Age 11–12		Age 7–8		Age 11–12	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Male sex	1.58	1.07–2.33	1.18	0.83–1.69	1.69	1.16–2.45	1.29	0.94–1.77	1.25	0.96–1.64	1.11	0.83–1.50
Family history of asthma	3.04	2.07–4.47	2.78	1.96–3.94	3.05	2.11–4.40	2.52	1.84–3.46	2.40	1.82–3.16	2.48	1.84–3.34
Breast feeding ≤ 3 months	1.26	0.81–1.97	1.12	0.73–1.72	1.32	0.86–2.01	1.32	0.91–1.92	–	–	–	–
Birth weight <2500 g	2.57	1.22–5.40	0.91	0.37–2.28	2.23	1.07–4.66	1.54	0.76–3.14	2.11	1.18–3.77	0.75	0.33–1.71
Respiratory infections	2.14	1.40–3.27	2.20	0.90–5.37	2.46	1.62–3.73	1.88	0.82–4.34	2.83	2.09–3.84	6.74	3.50–12.96
Mother current smoker	1.50	0.99–2.26	1.41	0.95–2.08	1.47	0.99–2.18	1.50	1.06–2.11	1.21	0.90–1.62	1.42	1.03–1.97
Cat ever at home	0.71	0.43–1.17	0.54	0.34–0.86	0.70	0.44–1.14	0.67	0.46–0.99	0.86	0.62–1.19	0.70	0.49–1.00
Dog ever at home	0.99	0.65–1.51	0.78	0.54–1.13	0.91	0.61–1.37	0.95	0.69–1.31	0.96	0.71–1.28	0.91	0.67–1.23
Living in damp house	2.18	1.45–3.28	0.86	0.36–2.05	1.91	1.29–2.85	0.86	0.40–1.85	1.72	1.27–2.32	1.48	0.80–2.71
Living in apartment	–	–	–	–	–	–	–	–	1.28	0.95–1.72	1.16	0.84–1.62
Allergic sensitization	4.88	3.31–7.20	5.63	3.88–8.18	4.25	2.93–6.16	4.72	3.41–6.53	3.19	2.40–4.23	4.35	3.22–5.87
Citrus fruits/week												
≤ 2	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–
3–6			0.89	0.60–1.31			0.82	0.58–1.17			1.09	0.79–1.52
≥ 7			0.58	0.35–0.97			0.67	0.43–1.04			0.87	0.58–1.30

Allergic sensitization and a family history of asthma were the most important risk factors for a report of asthma, and the importance of the former tended to increase with age while the latter remained constant. Remission and relapses were common, and remission probability was strongly inversely related to allergic sensitization. The participation was high, and hence the studied sample is representative of the population.

Among the 7- to 8-year-old children, the boy-to-girl ratio for *current asthma* was 1.5, decreasing to 1.3 at age 11–12. Prevalence of *physician-diagnosed asthma* increased from age 7–8 to 11–12 but with a continuously decreasing magnitude of increase. Over the same time period the prevalence of *wheeze last 12 months* decreased. Most likely this reflects a shift in the phenotype of wheezing disorders as the small children age to preteens. It seems that a larger proportion of younger children not diagnosed with asthma experience wheezing while wheeze in older children is more frequently diagnosed as asthma. This finding illustrates the complexity of the problem. Are childhood wheezing disorders aligned along a continuous scale of severity, or do they reflect essentially different conditions?

The evaluation of life-time prevalence shows the proportion of the population that ever has been affected by a certain condition. This is of interest both from the individual's perspective, and from a public health standpoint. Nearly one-tenth of the children at age 11–12 had ever had a physician diagnosis of asthma, and more than one-third had at some time reported wheeze, numbers similar to findings in the Isle of Wight (14) and New Zealand (8). A substantial proportion of the children reporting symptoms (340 of the 729 *ever wheezers*) at age 7–8 denied ever having had symptoms in at least one later

questionnaire. This is one of the important features of yearly follow-ups: mild asthma symptoms are easily forgotten, a problem previously discussed for adults (24). The proportion of *ever wheezers* was high and asthma symptoms often precede the diagnosis by years. Our finding has implications for epidemiological studies, especially when discussing different asthma phenotypes and their relation to age.

There is no generally accepted definition of remission of asthma. With our definition, i.e. free from asthma medicines and symptoms, the yearly remission was about 10%, but nearly half of those in remission had subsequent relapses. Relapses may also occur later, as was reported by Sears et al. (8), who found that of wheezers from childhood to age 26 only about half had persistent wheezing from onset. In a large British birth cohort study, only 35% of subjects with asthma or wheeze in childhood were in complete remission at age 33 (25).

The finding that allergy was not only a strong risk factor for asthma but also inversely associated with remission of asthma is consistent with other studies (8, 12, 14). Remission of allergic sensitization only occurred among nonasthmatic children in this cohort. As the progression from allergic sensitization to allergic asthma has not been fully elucidated, it is worth noting that incidence of allergic sensitization was twice as high among incident asthmatics compared with those without incident asthma. Interestingly, Crestani et al. found that parental asthma was a predictor of allergic sensitization in children, regardless of asthma in the child and parental atopy status (26).

In addition to the discussion of the complex relationship between allergy and asthma, it seems that some individuals are susceptible to both allergic sensitization

and wheezing, genetically or by environmental exposure. Our findings emphasize the difference between the allergic and nonallergic asthma phenotypes and their associated risk patterns in school age children.

For *current asthma* allergic sensitization and a family history of asthma remained the most powerful determinants also at age 11–12 (6). The importance of allergic sensitization tended to increase over the 4-year period. The finding that early onset asthma has higher remission probability than late onset asthma was attributable to the increasing importance of allergy (8, 12, 14). This we think, advocate phenotyping of childhood wheezing conditions on the basis of proposed causality, rather than onset age. The significant association between family history of asthma and asthma in the child from age 7–8 to age 11–12 shows that inheritance is consistently important over time during this period in life. Family history of asthma is an equally important risk factor for allergic and nonallergic asthma alike, even when corrected for reported family history of allergy (19).

Severe respiratory infections are strongly associated with asthma (15, 27). Evidence supporting the mechanisms is most consistent for respiratory syncytial virus (27–29). Respiratory infections have been proposed to induce persistent nonallergic childhood wheeze. In our study, this association was significant for *current asthma* only at age 7–8 and limited to nonallergic children (19), raising questions about the remission probability for these children. Several of the known risk factors significantly associated with wheeze and asthma at age 7–8 were no longer significant when the children were 4 years older. This change may be explained by the increasing importance of allergic sensitization, but we cannot exclude the possibility of unknown risk factors coming into play with increasing age.

The ‘protective’ effect of living with a pet on the development of allergy and asthma has been examined in this cohort and discussed previously (9, 20), and has been reported from other studies in different populations (30–32). When stratified by family history of asthma in our cohort, the effect remained significant and was even more pronounced among children with a family history of the disease (9). In this study this effect was significant only for cat, not for dog, and only at age 11–12, suggesting a more pronounced effect in preteenage children, similar to findings by Hesselmar et al. (30). To decrease selection bias, the variable ‘cat/dog ever at home’ was used, thus including subjects keeping a cat/dog before onset of asthma. In addition multivariate analysis included the variable ‘family history of asthma’ which should be controlling for the confounding effect of asthmatic parents not keeping a furred pet, while passing on the susceptibility for asthma to their children. Including a family history of allergy in the multivariate model only changed OR for cat ever at home from 0.54 to 0.56, suggesting that the inverse relationship is not due to allergic parents choosing to avoid keeping cats.

Interestingly, there was an inverse relationship between the variable ‘consumption of citrus-fruits’ and asthma development. Possibly, citrus-fruit consumption reflects a multifactorial ‘healthy lifestyle’, or avoidance, as allergic children may avoid citrus-fruits because of hypersensitivity. However, low Vitamin C levels in subjects with asthma have been reported previously (33), and vegetable consumption in general has shown an inverse relationship to asthma in children (34).

Wheezing in the last 12 months had the same risk factor pattern as did current asthma both at age 7–8 and 11–12 but with lower ORs which most likely reflects lower specificity. Although there is a methodological overlap between the dependent variables, the absence of a difference in risk factor patterns argues that they are aligned along a scale of severity, rather than attributable to different phenotypes.

From this overview of a northern Swedish population followed from age 7–8 to 11–12, we confirm the high prevalence of asthma and allergy found internationally. The large cohort size and yearly follow-ups made in-depth risk factor analyses possible. These analyses clearly identified allergic sensitization and a family history of asthma as the strongest determinants of childhood asthma. The effect of a family history of asthma was constant from age 7–8 to 11–12, while the effect of allergic sensitization tended to increase with age. Parallel to this development occurred a major shift with several of the known risk factors associated with asthma at age 7–8 no longer associated with asthma when the children were 4 years older. The reason for this shift likely includes a stronger association with allergic sensitization at this age and possibly other factors leading to the development of asthma in children already sensitized. The negative association between allergic sensitization and asthma remission partly explains why late onset asthma tends to persist. This along with our finding that prevalent asthma is a negative predictor of remission of allergic sensitization suggests that the relationship between allergy and asthma goes beyond the classical causality discussion, where allergic sensitization simply precedes asthma. Further investigation must take this into consideration when dealing with the allergic and nonallergic asthma phenotypes.

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